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Attorney Docket No. 9013.63 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Pickard et al.
Application No.: 10/511,455
Filed: August 29, 2005
For: *Schizophrenia associated genes*

Confirmation No.: 2347
Group Art Unit: 1634
Examiner: S. Kapushoc

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132 OF BENJAMIN SIMON PICKARD

Sir:

I, Benjamin Simon Pickard, do hereby declare and say as follows:

1. I am a named inventor on United States Application No. 10/511,455 ("the '455 application") and of the subject matter claimed therein.

2. I have a PhD from The University of Edinburgh in the UK. I am a Group Leader at The University of Edinburgh, UK. I have been conducting research in the area of Psychiatric Genetics for nine years and have authored or co-authored more than 20 publications related to this area.

3. A person of ordinary skill in the art would be able to identify a human subject having a susceptibility to schizophrenia and/or affective psychosis using the information provided in the specification. Using the GRIK4 gene locus as a reference point, and patient cell/DNA material as the experimental sample, that person would be able to use standard laboratory cytogenetic, chip array or molecular genetic techniques (e.g., sequencing or genotyping assays) to identify any one of several possible molecular lesions. These could include further gross or fine (copy number variation) chromosome abnormalities or functional sequence changes ('mutations').

Chromosomal abnormalities generally reduce the operational quantity of the damaged gene and its messenger RNA (mRNA) leading to the pathological reduction of functional protein product. Other mutations can also affect gene/mRNA levels or the properties of the encoded protein such that it no longer functions appropriately. Page 33, line 11 to page 38, line 1 details the data obtained from the analysis of a subject suffering from chronic schizophrenia. The text on page 34, line 33 to page 35, line 13 states that the identified 11q23.3 breakpoint is located upstream of exon 2 of the GRIK4 gene sequence and that breakpoints located here (or indeed anywhere between exons 1a/a'/1b and 3) would truncate all putative transcript forms such that no receptor function could be encoded. As such, the functional consequences of the detected chromosomal abnormality are reduced GRIK4 gene dosage (see page 35, line 22) and possibly reduced glutamate receptor subunit expression as per the "glutamate hypothesis" (see page 35, line 13, page 36, lines 14-16 and 24-28).

The identification of a GRIK4 chromosomal rearrangement associated with schizophrenia provides a *de facto* link between this gene and mental illnesses, of which schizophrenia and/or affective psychosis are examples. This approach has been previously and widely used to identify links between genes and disease (e.g., Duchenne Muscular Dystrophy, Neurofibromatosis and many cancers). Hence, a person of ordinary skill applying the techniques described above would be scientifically justified in assuming that the existence of a functionally significant chromosomal abnormality or mutational damage to the GRIK4 gene would be likely to cause, or alter risk of/susceptibility to, psychiatric conditions typified by schizophrenia/affective psychosis.

4. At the time of filing this application, techniques which enabled the detection of relative mRNA levels and immunoassays for detecting gene products, were routine. Furthermore, we have recently shown (Pickard *et al.*, Proc Nat Acad Sci, USA (2008) in press) that a relatively common 14 base deletion within the GRIK4 mRNA results in altered mRNA levels and that this alters risk of bipolar disorder - a psychiatric illness within the diagnostic boundaries defined above. Subsequently, we have shown in post mortem brain tissue that this mRNA difference is also reflected in protein abundance changes. Hence, a person of ordinary skill in the art would be able to use standard laboratory methods for the quantification of mRNA/protein levels of GRIK4

as a proxy for underlying chromosomal abnormalities/mutations to assess potential risk of mental illness.

5. Throughout, we use the combined terms 'schizophrenia and/or affective psychosis' and 'chromosome abnormalities and/or mutations'. The former term denotes the accepted clinical/scientific understanding that psychiatric illnesses exist as a spectrum of closely related conditions which have common aetiologies and pathologies but are subjectively categorized by current diagnostic practices. It is appropriate, therefore, to suggest that GRIK4 may contribute to any one of these conditions in any given individual. The latter term refers to the well-established biological/genetic observation that there are many forms of damage to a gene (e.g., chromosomal abnormality and sequence mutation) which similarly affect the encoded protein's function. Hence, it is appropriate to identify and use, in the scientific/clinical environment, any one of these forms of genetic damage for the purpose of defining an individual's risk of psychiatric condition.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

16th September 2008

Benjamin Simon Pickard **Date**